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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/678,961	10/03/2003	Michael R. Slater	016026-9457 US00	7299

91007 7590 10/28/2010
Michael Best & Friedrich LLP
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EXAMINER	
VOGEL, NANCY TREPTOW	

ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
10/28/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/678,961	SLATER ET AL.
	Examiner	Art Unit
	NANCY VOGEL	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 09 August 2010.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,3,4,6,7,9-13,36,84,85 and 87-111 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,3,4,6,7,9-13,36,84,85 and 87-111 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 10/20/10 - 3.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3, 4, 6, 7, 9-13, 36, 84, 85, 87-111 are pending in the case.

Receipt of the Information Disclosure Statement on 10/20/10 is acknowledged.

Reference DE 10038573 is crossed through since it is not in English and no explanation of its relevance has been submitted.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 4, 6, 7, 9, 10, 36, 84-109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parrott et al. (6,096,523) in view of Santi et al. (US 2004/0166567), Berg and Berg (1996), "Transposable element tools for microbial genetics" Escherichia coli and Salmonella Neidhardt. Washington, D.C., ASM Press. 2: 2588-2612), Merril et al. (US Patent 5,811,093) and Holt (http://wheat.pw.usda.gov/~lazo/methods/donis/plasmid/plsmid10.html) disclose.

Parrott et al. disclose a method for directional subcloning of DNA fragments comprising providing a first vector comprising a first and second infrequent restriction site, between which a DNA of interest is cloned, wherein restriction of said first and second restriction sites does not generate ends complementary to each other, and providing a second vector comprising a third and fourth enzyme sites, wherein the third restriction enzyme generates single stranded ends complementary to the first site, and a fourth restriction enzyme which generates ends that can be ligated to the ends generated by the second restriction enzyme, which permit the oriented joining of the first linear DNA fragment to the second linear DNA fragment (see col. 5, lines 35- col. 6, line 21; see col. 7, lines 23- col. 8 line 5, in which a shuttle vector having a DNA segment of interest is between a CeuI and a TliI site, and in which the vector is restricted with CeuI and TliI, and then inserted into a docking vector which is cut with CeuI and TliI enzymes). The reference discloses that any two rare restriction sites may be used in the first and the second vector, including different ones (col. 5 lines 28-65; col. 7 lines 24- col. 8 line 5). The reference discloses that any vector known in the art may be used, and that factors affecting vector choice are known in the art, including type of replicon and nature and location of selection marker (col. 6, lines 35-54). The difference between the reference and the instant claim is that a second selectable marker which is distinguished from the first marker is present on the second vector, and the first restriction enzyme generates a 3' TA overhang, and a counter selectable marker is present on one of the vectors, and sequences including a portion of the overhang generated by the third restriction enzyme include one or more codons that after oriented joining are in-frame with the open reading frame, thereby encoding an N-terminal fusion with the gene product encoded by the open reading frame, and/or wherein sequences forming a portion of a 3' to the cleavage site generated by the fourth restriction enzyme include one or more nucleotides for a stop codon that after oriented joining are in-frame with the open reading frame or for one or more codons that after oriented joining a re in-frame with the open reading frame , thereby encoding a C-terminal fusion with the gene product encoded by the open reading frame.

However, Santi et al. (US 2004/0166567) teach methods for subcloning using two different vectors having different selectable markers, for the selection of a vector construct of interest. The reference discloses a method for directional subcloning of DNA fragments comprising using selectable markers on each of two vectors; a gene of interest is cut from a first vector using restriction enzyme sites on either side of the gene of interest, and this fragment is ligated into a second vector which has been cut at two restriction sites on either side of a selectable marker (see Fig. 3, 5, see page 15 paragraphs 0182-0186). The reference discloses restriction endonuclease which may be used, including PvuI, SgfI, PmeI, PacI, all of which are well known commercially available restriction enzymes, with well known recognition sites, which are well known to be useful in particular combinations due to compatible single stranded overhangs. SgfI leaves a 3’ TA end. These manipulations of DNA vectors are routine methods commonly practiced in the art and well known to those of skill in the art. Berg et al. disclose counterselectable markers which may be used on vectors for selection purposes. Merril et al. (US Patent 5,811,093) disclose methods of genetic engineering in which a DNA portion is cloned into a vector to create for instance, 3' fusion protein encoding regions (see col. 6 line 60). Holt (http://wheat.pw.usda.gov/~lazo/methods/donis/plasmid/plsmid10.html) disclose methods of ligating fragments that contain one blunt end and one end with a single stranded overhang, using standard methods of ligation (i.e. “one ended blunt ligations).

It would have been obvious to one of skill in the art to have modified the disclosure of Parrott, by including selection markers on both of two starting vectors, and by using any particular restriction enzyme sites, as taught by Santi et al., since both references disclose methods of inserting any DNA fragment of interest from a first vector, into a second vector in a directional manner, using selectable markers and appropriate restriction enzyme recognition sites which yield compatible and/or ligatable ends. One would have been motivated to do so by the desire to select for and/or against the presence of any particular DNA fragment in the final construction, a technique which is well known and routine in the art of DNA manipulation. The construction of desired vectors using restriction enzymes is routine and well known in the art, and virtually any desired construct is routinely made using such well known techniques as directional cloning and subcloning, and selection using selection markers. It would have been obvious to have included a counterselectable marker on the second vector, since such markers are well known to be generally applicable to vector selection. It would have been obvious to one of ordinary skill in the art to have included in the method, a vector comprising portions of a protein encoding region at the 5' or 3' end of a restriction site into which DNA of interest is inserted, for the purpose of creating an in-frame fusion protein, as taught by Merril et al. It would have been further obvious to have utilized blunt end cutting restriction sites in the method, since Holt discloses that ligation of fragments containing one restriction site that leaves a single stranded overhang, and one blunt end, to a similar fragment, is known in the art and can be accomplished using standard well known methods. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Applicant's arguments filed 4/15/10 have been considered but have not been found convincing.

Applicants argue that the combinations of the references fail to teach each and every element of the claimed invention, arguing that the references do not teach using a lethal gene, let alone barnase. Furthermore, applicants argue that the references do not teach the use of particular combinations of restriction enzymes, and restriction sites that form a stop codon in frame with the open reading frame or a C-terminal fusion. However, Berg cited above teaches use of counter selectable markers, including SacB or kil (page 140), which are disclosed in the specification to meet the limitation of a "lethal" gene. Furthermore, the cited references teach the use of different restriction sites, especially for directional cloning, in which an insert always is ligated in a particular desired orientation. The use of any particular restriction enzyme site, termination signals and fusions in vectors are generally well known in the art as disclosed in the references. The cited references teach directional cloning, using rare cutters, leaving desired overhangs, or blunt ends, in addition to the use of selectable lethal markers, vectors that result in in-frame fusion protein encoding sequences. Each of these elements is known in the art, and the combination of these elements into vectors in a method of genetic manipulation, was known in the art. The art of genetic engineering generally involves the construction of vectors or plasmids or constructs, using individual building blocks such as restriction sites, markers, open reading frames, etc.,

Claims 1, 3, 4, 6, 7, 9-13, 36, 84-109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parrott et al. (6,096,523) in view of Santi et al. (US 2004/0166567) Berg et al., Merril et al. (US Patent 5,811,093), Holt (http://wheat.pw.usda.gov/~lazo/methods/donis/plasmid/plsmid10.html) as applied to claims 1, 3, 4, 6, 7, 9, 10, 36, 84-109 above, and further in view of Innerarity et al. (US 20010029027).

Parrott et al. and Santi et al. and Berg et al., Merril et al., Holt, are cited for the reasons set forth above.

The difference between the references and the instant claims is that sites for one or more restriction enzymes in the open reading frame are protected by methylation so as to prevent digest, and prior to methylation the flanking sites for the first or second restriction enzyme site are contacted with an oligonucleotide complementary to the flanking restriction enzyme site and RecA. However, Innerarity et al. disclose a method of protecting restriction sites using methylation, protecting other restriction enzyme sites by contact with an oligonucleotide complementary to said enzyme sites and RecA (see paragraph 150). This method of protection of restriction sites using methylation, and protection from methylation by binding an oligonucleotide and RecA to a restriction site, are well known in the art to be useful for the manipulation and construction of vectors having desired fragments, as disclosed by the reference. It would have been obvious to one of ordinary skill in the art to have combined the teaching of Innerarity et al., which discloses methylation of restriction sites which one does not want restriction cutting to take place at, along with protection of sites which one does want said cutting to take place at using oligonucleotide/RecA binding, and the teachings of Parrott et al. and Santi et al., since all three references disclose methods of constructing vectors of interest using restriction enzymes. One would have been motivated to do so by the desire to cut particular fragments out of a vector, without cutting the fragment internally. Such a cloning/subcloning method is routine in the art and would have been obvious to one of ordinary skill in the art, as evidence by the extensive and routine use of such techniques in the art of biotechnology. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Applicants have presented arguments addressing this rejection together with the above rejection.

For the reasons set forth above, the rejection is maintained.

The following is a new rejection necessitated by applicant's amendment to the claims:

Claims 1, 3, 4, 6, 7, 9-13, 36, 84-1111 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parrott et al. (6,096,523) in view of Santi et al. (US 2004/0166567) Berg et al., Merril et al. (US Patent 5,811,093), Holt (http://wheat.pw.usda.gov/~lazo/methods/donis/plasmid/plsmid10.html), Innerarity et al. (US 20010029027) as applied to claims 1, 3, 4, 6, 7, 9-13, 36, 84-109 above, and further in view of Mead et al. (US Patent 6,709,861)

Parrott et al. and Santi et al. and Berg et al., Merril et al., Holt, Innerarity et al. are cited for the reasons set forth above.

The difference between the references and the instant claims is that the lethal gene is barnase.

However, Mead et al. (6,709,861)teach vectors comprising the barnase gene for selection purposes (see col. 73-75). It would have been obvious to one of ordinary skill in the art to have inserted the barnase gene, bounded by restriction sites, into a vector, in order to have a selection marker. The use of the barnase gene for its known purpose of selection would have been obvious to one of ordinary skill in the art. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NANCY VOGEL whose telephone number is (571)272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NANCY VOGEL/
Primary Examiner, Art Unit 1636

NV
10/20/10